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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/537,682	06/03/2005	Jacques F. Banchereau	BHCS:1028	8543

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EXAMINER	
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ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/537,682	BANCHEREAU ET AL.	
	Examiner	Art Unit	
	GERALD EWOLDT	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 November 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed 11/24/10 in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's amendment and remarks filed 11/24/10 have been entered.

2. Claims 44-50 are under examination.

3. In view of Applicant's amendments the previous rejections under 35 U.S.C. 102(b) and (e) have been withdrawn.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 44-50 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As set forth previously, the claims are vague and indefinite in the recitation of "TNFα". Regarding "TNFα", the specification defines TNFα as, "any TNF or TNF-like protein which functions as an activator in the methods of this invention". By this definition it is unclear then if Applicant is attempting to define other cytokines such as IL-4 as TNFα, given that IL-4 has the same effect on monocytes in the claimed method. Accordingly, the metes and bounds of the claims cannot be determined.

Applicant's arguments, filed 11/24/10, have been fully considered but are not found persuasive. Applicant argues that the claims are now limited to "human TNFα molecules *and their equivalents*" (emphasis added).

TNFα "equivalents" have not been defined. Also note that the claims recite "a" human TNFα molecule, thus, indicating that there are multiple human TNFα molecules encompassed by the method of the instant claims. Accordingly, the metes and bounds of the claims still cannot be determined.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 44-50 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

A set forth previously, There is insufficient written description to show that Applicant was in possession of the tumor necrosis factor alpha (TNFα) of the claims.

At page 17 the specification defines TNFα as, "any TNF or TNF-like protein which functions as an activator in the methods of this invention". A review of the specification shows that even the TNFα employed in the Examples, e.g., page 21, is undefined as to its particular source, i.e., species or whether or not it is actually TNFα or a TNF-like protein. Clearly then no species of the thousands of TNFα's are actually described. No common TNFα structure is defined and neither is a common function. While it could be assumed that the common function might be the ability to induce the differentiation of monocytes into dendritic cells (DCs), the specification merely discloses that TNFα's, "function as an activator in the methods of this invention". Regarding the "TNF-like proteins" of the claimed method, none are defined nor disclosed. Clearly, neither specific structure and function, nor an adequate number of representative species of TNFα, are disclosed in the instant specification. One of skill in the art would therefore conclude that the specification fails to adequately describe TNFα. See *Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398.

Applicant's arguments, filed 11/24/10, have been fully considered but are not found persuasive. Applicant argues that the claims are now limited to "human TNFα molecules *and their equivalents*" (emphasis added).

While Applicant was clearly in possession of the TNFα purchased from R&D Systems, no TNFα "equivalents" have not been disclosed. And while a common function is disclosed a common structure is not.

8. Claims 44-50 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in

the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As set forth previously, The instant claims encompass a method for generating DCs from monocytes employing GM-CSF and TNFα. This method has been tried in the prior art and did not result in mature DCs. See Pickl et al. (1996) wherein the authors compared the resulting products of monocytes matured in GM-CSF and IL-4 to the products of monocytes matured in GM-CSF and TNFα. As stated in the Abstract, "Only GM-CSF plus IL-4 cultured cells [monocytes] were found to be potent stimulators in allogeneic and autologous MLR…", i.e., only the GM-CSF plus IL-4 cultured cells were mature DCs. At page 3853 and Figure 5 the reference further teaches that the GM-CSF and TNFα cultured monocytes appeared to be proliferating, which would not be a characteristic of mature DCs. Figure 9 shows that GM-CSF and TNFα cultured monocytes were only minimally better stimulators of primary T cell responses than were freshly isolated monocytes. It appears then that culture of monocytes in GM-CSF and TNFα results in only partially differentiated DCs and not the mature DCs of the claims.

New note: there is no evidence of record that any antigen presenting cells other than dendritic cells e.g., B cells, could be produced by the method of the instant claims.

Applicant's arguments, filed 11/24/10, have been fully considered but are not found persuasive. Applicant argues that the failure of Pickl et al. cannot be allowed to place additional burdens on the Applicant.

Pickl et al. performed the method of the instant claims as claimed. Said method did not result in a functional DC. While Applicant's may have succeeded in producing functional DCs there must be more required of the method of the instant claims than simply mixing monocytes, TNFα, GM-CSF, and antigen, i.e., the single step of Claim 44.

Applicant demands support for the "Official Notice" that it is well established that activation of T cells in an MLR context is much easier to perform than the activation of T cells in an antigen-specific context.

While Applicant is expected to be of skill in the art, and the fact that any elementary immunology textbook should teach that it is well established that activation of T cells in an MLR context is much easier to perform than the activation of T cells in an antigen-specific context, a relevant portion of Paul's *Fundamental Immunology* (1999) has been attached. As taught therein, as many as 2% of a total T cell population might take part in a MLR response, while only approximately 1 in 10,000 (0.01%) of a total population of T cells would be expected to

react to any specific antigen. That would be a response of at least 2 orders of magnitude less for an antigen-specific response than for a MLR response.

Applicant alleges that the addition of "antigenic material" to the culture medium allowed them to succeed where Pickl et al. failed.

Applicant is advised that "antigenic material" (i.e., material capable of being bound by an antibody) is always present in any culture medium as culture medium comprises multiple proteins and polysaccharides. While it is possible that the unexpected results are the result of the specific "antigenic material" used by Applicant in the examples of the specification, the claims are not so limited.

In an additional argument rendered moot by the withdrawal of the previous rejections under 35 U.S.C. 102, Applicant alleges, "Applicants submit that the term antigen is commonly understood to be a molecule intended to or capable of being recognized by the immune system; i.e., a substance that is capable, under appropriate conditions, of inducing a specific immune response and of reacting with the products of that response" citing wikipedia.com, answers.com, and thefreedictionary.com.

Applicant is advised that online, open source, websites comprise unreliable sources of information. Immunology textbooks such as Paul's cited above are recommended. Regarding antigens, they are generally defined as molecules capable of being bound by antibodies. Immunogens are generally defined as molecules capable of generating an immune response.

9. The following are new grounds for rejection.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 44-50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, specifically, the recitation of

"antigenic material that induces an immunogenic response" is vague and indefinite as the production of an immune response is context dependent, i.e., a material might be capable of inducing and immune response in one context but not in another. Additionally, the method of the instant claims is performed in a single *in vitro* step wherein no immune response-inducing conditions are recited in the claims, with the possible exception of Claim 49. Accordingly, the metes and bounds of the claims cannot be determined.

12. Claims 44-50 are rejected under 35 U.S.C. 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a written description rejection for the introduction of new matter into the claims.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically:

A) The method of Claim 49 wherein a T cell is present in the method of producing an antigen-loaded antigen presenting cell (added in the amendment of 6/03/05).

B) The method of Claim 44 now reciting the newly added limitation that the antigenic material "induces an immunogenic response".

No specific support for either of the limitations has been cited and none has been found.

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 44-47 and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhou and Tedder (1996) in view of Morse and Lyerly (1998, IDS).

Zhou and Tedder teach a single step method of producing human dendritic cells from human monocytes comprising culturing monocytes in GM-CSF and TNFα (see particularly column 8, lines 1-6) in combination with cyclosporin (see particularly page 2588, column 2).

The reference teaching differs from the claimed invention only in that it does not teach the presence of the antigen of interest in the culture nor dying cell bodies or fragments as the antigens.

Morse and Lyerly teach the loading of dendritic cells for therapeutic use in humans with various immunogenic antigens including peptide or protein antigens and tumor extracts (dying cell body fragments).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to perform the single step method of producing dendritic cells from the monocytes of Zhou and Tedder employing GM-CSF and TNFα further employing the various antigens of Morse and Lyerly. The choice of antigen would simply depend on the context, e.g., the use of tumor antigens or tumor cell extracts for the treatment of cancer. Further, the ordinarily skilled artisan would have been motivated to simply add the antigen to the cell culture in the single step of the process to streamline said process as there would be no reason to add it later, i.e., produce the dendritic cells in one process and add the antigen in a later process. Using cell extracts in particular, as the dendritic cells passed through the immature state they would have been more able to internalize and process the antigen than would mature dendritic cells that would then be capable of inducing an immune response to the antigen(s).

15. No claim is allowed.

16. **Please Note:** Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact

the Electronic Business Center (EBC) at 866-217-9197 (toll-free). Additionally, the Technology Center receptionist can be reached at (571) 272-1600.

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